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Session 4 *Oral Abstract Session*

Antiretroviral Chemotherapy: New Agents

Session Time: Monday, 10 am - 12:30 pm

Room 6A-B

10:00 1. SCH C: Safety and Antiviral Effects of a CCR5 Receptor Antagonist in HIV-1- Infected Subjects

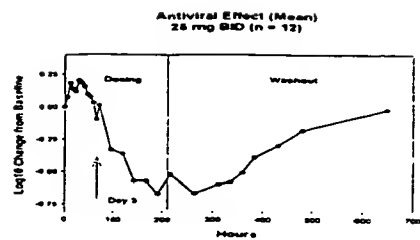
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Background: SCH C is an orally bioavailable CCR5 receptor antagonist with potent *in vitro* antiviral activity against a broad selection of primary HIV-1 isolates. The safety and tolerability as well as pharmacokinetic profile have been described in healthy volunteers to doses as high as 600 mg as a single dose (mean C_{max} ~2100 nM) and 400 mg/day as multiple (14 days) doses (mean C_{max} ~1400 nM). Prolongation of the QTc interval was noted at the 600-mg single dose and at the 400-mg/day multiple dose level. The *in vivo* potential for antiviral effects of SCH C is currently being investigated in an ongoing, sequential rising dose trial (12 subjects/group) as monotherapy with daily doses of 50 mg, 100 mg, and 200 mg in HIV-infected subjects

Methods: 12 adults chronically infected with HIV 1 currently on no antiretroviral agents and with CD4+ cell counts above 250/mm³ were administered 25 mg SCH C orally every 12 hours for 10 days. HIV-1 RNA levels were determined every 6 hours for 72 hours and then every 24 hours for the remaining 10 days of dosing. In addition, periodic HIV-1 RNA levels were determined during 18 days of follow-up. Subjects had SI/NSI phenotyping prior to dosing, at the end of dosing and at follow-up. Subjects with an SI phenotype at baseline were excluded from participation. The pharmacokinetic profile was determined.

Results: SCH C was safe and well tolerated. Preliminary analysis of the pharmacokinetic profile was similar to healthy volunteers with mean C_{max} and C_{min} levels at steady state of approximately 140 nM and 90 nM, respectively. The figure shows the antiviral effects of SCH C over the 10 days of dosing and during washout. As shown there is a short lag time in effect as well as a prolonged effect following cessation of dosing. 10 of 12 subjects had at least a 0.5 log₁₀ reduction from baseline during dosing, with 4 subjects achieving 1.0 log₁₀ or greater reduction.



Conclusions: Preliminary data with SCH C supports the CCR5 receptor as a viable target for antiretroviral therapy.

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